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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/367,496	11/24/99	AGUERA M	P06473US0/TP

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	9

DATE MAILED: 09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/367,496	Applicant(s) AGUERA ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7, 9, 10, 14-17 and 20-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,14-17 and 20-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply* .

DETAILED ACTION

1. The election without traverse filed on July 11, 2001 in Paper No. 8 is acknowledged and has been entered.

2. The amendment filed on July 11, 2001 in Paper No. 8 is acknowledged and has been entered. Claims 8, 11-13, 18, and 19 are canceled. Claims 5, 10, and 17 are amended. Claims 20-35 are added.

3. Claims 1-7, 9, 10, 14-17, and 20-35 are pending in the application and are currently under prosecution.

Priority

4. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It does not identify the citizenship of each inventor.

Specification

6. The amendment filed July 11, 2001 in Paper No. 8 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 USC § 132 states that no amendment shall introduce new matter into the disclosure of the invention. There appears to be added material that is not supported by the original disclosure;

specifically, there appears to be no support in the specification, as originally filed for the "diagnostic substrate" of added claims 30-32.

Applicant is required to cancel the new matter in the reply to this Office Action.

Sequence Rules Compliance

7. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given three (3) months from the date of this Office Action within which to comply with the sequence rules under 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Objections

8. Claims 1, 3, 4, 6, 7, 16, 17, 23, and 28 are objected to because of the following informalities: Claims 1, 3, 4, 6, 7, 16, 17, 23, and 28 are drawn to the subject matter of non-elected inventions. Appropriate correction is required.

Additionally, it is noted that if claims 1, 4, and 16 are amended to recite the required limitation to the subject matter of the elected invention, claims 2, 5, and 17, respectively, would be objected to because of the following informalities: Claims 2, 5 and 17 would be objected to under 37 CFR 1.75(c), as being of improper dependent

form for failing to further limit the subject matter of previous claims 1, 4, and 16, respectively, from which claims 2, 5, and 17 depend. Accordingly, Applicant would then be required to cancel the claims 1, 5, and 17.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claim 10 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-7, 9, 10, 14-17, and 20-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a polypeptide, which the specification teaches comprised the amino acid sequence set forth in SEQ ID NO: 8. According to the specification, SEQ ID NO: 8 is the amino acid sequence of a protein encoded by a human cDNA molecule, which consists of the polynucleotide sequence set forth in SEQ ID NO: 7.

The teachings of the specification cannot be extrapolated to the enablement of the invention because there are discrepancies in those teachings, which would confuse the skilled artisan and therefore the skilled artisan would be unable to practice the claimed invention with a reasonable expectation of success. Consequently, the skilled artisan would be forced to perform undue experimentation in order to practice the invention.

It is noted that while the Sequence Listing teaches that the claimed polypeptide has an amino acid sequence, which is set forth in SEQ ID NO: 8 of the Sequence Listing, the specification teaches that the claimed polypeptide has an entirely different amino acid sequence (page 20, lines 20-35; Figure 12). Furthermore, it is appropriately noted that in Applicants previously placed the amino acid sequence of the same polypeptide, or at least a polypeptide that that shares the designation ULIP-4 in a public database (Database GenBank Accession No. Y10976, Byk, et al, Direct Submission, 03 February 1997). The amino acid sequence of GenBank Accession No. Y10976 differs from SEQ ID NO: 8 at position 56. While the identity of the nucleotide at position 197 of the mRNA sequence encoding the amino acid sequence is not disclosed, because the other two nucleotides within the same codon (i.e., nucleotide positions 198 and 199) are known, it is clear that the amino acid at position 56 of the polypeptide cannot be histidine and is very likely either lysine or glutamic acid. Hamajima, et al (*Gene* **180**: 157-163, 1996) published the amino acid sequence of a polypeptide that is nearly identical to the amino acid sequence of the claimed polypeptide, with the exception of the residue at position 56 (Database GenBank Accession No. AB006713). A human mRNA molecule encodes the polypeptide of Hamajima, et al also, but its polynucleotide sequence encodes lysine at position 56. With respect to the amino acid sequence of ULIP-4 shown in Figure 12, the specification discloses that the amino acid at position 56 is almost certainly a lysine.

In view of the discrepant teachings of the specification and also in view of obvious inconsistency between the specification and other disclosure made by the Applicants, the specification cannot be considered enabling under 35 USC § 112, first paragraph.

Applicants are invited to resolve the inconsistency, but are cautioned against the introduction of new matter by amending the specification, including the claims.

13. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for using the polypeptide of SEQ ID NO: 8 or derivative thereof to detect the presence of anti-CV2 antibodies in a biological sample, wherein said sample is blood serum or cerebrospinal fluid (CSF), does not reasonably provide enablement for a method for using any fragment of the polypeptide of SEQ ID NO: 8 or a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 7 to detect the presence of anti-CV2 antibodies in any biological sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 10 is drawn to a method for using the polypeptide of SEQ ID NO: 8, a derivative of SEQ ID NO: 8, a fragment of SEQ ID NO: 8, or a nucleic acid comprising the polynucleotide sequence of SEQ ID NO: 7 to detect the presence of anti-CV2 antibodies in a biological sample.

The specification provides reasonable enablement for a method of detecting the presence of anti-CV2 antibodies in a biological sample, wherein said sample is acquired from a patient or animal and is either a blood serum sample or a CSF sample.

However, the teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims for the following reason:

The specification does not provide exemplification of the invention that is commensurate in scope with the claims. One skilled in the art would not expect that every fragment of the polypeptide of SEQ ID NO: 8 could be used to practice the invention, because it is reasonable to expect that some of the fragments of SEQ ID NO: 8 will not bind specifically to anti-CV2 antibodies. One skilled in the art cannot predict which fragments of the polypeptide of SEQ ID NO: 8 can be used to practice the invention; unless disclosed in the specification, those fragments that can be used in the

invention can only be identified empirically. The specification provides no guidance, which identifies which portion of the polypeptide binds the antibodies. The specification fails to disclose the epitopes of SEQ ID NO: 8 to which the antibodies bind. Accordingly, one skilled in the art is not provided with enough information to practice the invention with a reasonable expectation of success without first performing undue experimentation.

One skilled in the art would not expect the anti-CV2 antibodies to bind to a nucleic acid comprising the polynucleotide sequence of SEQ ID NO: 7 or for that matter, to any nucleic acid molecule, because the specification only teaches that the antibodies bind the polypeptide of SEQ ID NO: 8. Clearly, in this case, the specification fails to provide an enabling disclosure, because one skilled in the art would not be able to practice the invention commensurate in scope with the claims with a reasonable expectation of success.

One skilled in the art would not expect to be able to detect anti-CV2 antibodies in any biological sample. Certainly, there are numerous examples of tissues in which anti-CV2 antibodies would not be found, but the specification provides insufficient guidance with regard to this issue and therefore, for this reason also, the disclosure fails to meet the enablement requirement of 35 USC § 112, first paragraph.

14. Claims 9, 15-17, and 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition useful for the diagnosis of cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome, wherein the development of said pathology is contingent upon developing autoimmune disease, wherein said autoimmune disease is characterized by the presence in the serum of patients, of anti-CV2 auto-antibodies, which bind specifically to the polypeptide of SEQ ID NO: 8, wherein said composition comprises the polypeptide of SEQ ID NO: 8., does not reasonably provide enablement for a composition useful for the diagnosis, prevention, suppression, or treatment of *any* type of paraneoplastic neurological syndromes and/or the diagnosis, prevention, suppression, or treatment of a tumor, wherein said composition comprises the

polypeptide of SEQ ID NO: 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 14 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in vitro* diagnosis of cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome, wherein the development of said pathology is contingent upon developing autoimmune disease, wherein said autoimmune disease is characterized by the presence in the isolated serum of patients, of anti-CV2 auto-antibodies, which bind specifically to the polypeptide of SEQ ID NO: 8, wherein said method comprises contacting an isolated blood serum sample with the polypeptide of SEQ ID NO: 8., does not reasonably provide enablement for a method for the *in vitro* or *in vivo* diagnosis, prevention, suppression, or treatment of *any* type of paraneoplastic neurological syndromes and/or the diagnosis, prevention, suppression, or treatment of a tumor, wherein said method comprises contacting any sample isolated from a subject with the polypeptide of SEQ ID NO: 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 25-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 16 and 17 are drawn to a pharmaceutical composition comprising the purified polypeptide of SEQ ID NO: 8, a fragment of the polypeptide of SEQ ID NO: 8, or a biologically active derivative of the polypeptide of SEQ ID NO: 8. Alternatively, claims 16 and 17 are drawn to a pharmaceutical composition comprising a nucleotide, which encodes the polypeptide of SEQ ID NO: 8 or which is capable of hybridizing specifically with a nucleotide encoding the polypeptide of SEQ ID NO: 8. The claims encompass a pharmaceutical composition that has an undisclosed pharmacological effect and could be interpreted to be a composition for use in diagnosing, preventing, or treating any

pathology or ailment. However, in view of the specification, the claims appear to encompass a pharmaceutical composition that can be used for the diagnosis, prevention, suppression, or treatment of *any* type of paraneoplastic neurological syndrome and is not limited to a pharmaceutical composition useful for the diagnosis of cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome, wherein the development of said pathology is contingent upon developing autoimmune disease, wherein said autoimmune disease is characterized by the presence in the serum of patients, of anti-CV2 auto-antibodies, which bind specifically to the polypeptide of SEQ ID NO: 8, wherein said composition comprises the polypeptide of SEQ ID NO: 8. The claims also encompass a pharmaceutical composition useful for the diagnosis, prevention, suppression, or treatment of *any* type of tumor, wherein said composition comprises the polypeptide of SEQ ID NO: 8. Additionally, claims 16 and 17 encompass a pharmaceutical composition that is useful for the diagnosis, prevention, suppression, or treatment of *any* type of paraneoplastic neurological syndromes and which is also useful for the diagnosis, prevention, suppression, or treatment of *any* type of tumor, wherein said composition comprises the polypeptide of SEQ ID NO: 8.

Claim 9 is drawn to a composition comprising the polypeptide of SEQ ID NO: 8, but recites a limitation of intended use; the claim, therefore, clearly encompasses some of the same subject matter as claims 16 and 17. Claims 15 and 33-35 are drawn specifically to a kit that comprises the polypeptide of SEQ ID NO: 8, a derivative of the polypeptide of SEQ ID NO: 8, or nearly any fragment of the polypeptide of SEQ ID NO: 8. However, a kit is only as useful as the components of which the kit is composed. Recitation of the limitation that the component(s) (i.e., the polypeptide, derivative, or fragment and a means of visualization) be included in the kit provides no new feature of the physical structure of the component(s) that would limit the use of said component(s). Therefore, because claims 15 and 33-35 also recite a limitation of intended use, a use that is encompassed by claims 9, 16, and 17, claims 15 and 33-35 are interpreted reasonably to encompass some of the same subject matter as claims 9, 16, and 17. In other words, claims 9, 15, and 33-35 read on a composition or component of a kit that is

used for *in vivo* diagnosis of paraneoplastic neurological syndromes and/or tumors and which is administered as a pharmaceutical to a patient or other subject.

Claims 14 and 20-24 are drawn to a method for the diagnosis of *any* type of paraneoplastic neurological syndrome and is not limited to a pharmaceutical composition useful for the diagnosis of cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome, wherein the development of said pathology is contingent upon developing autoimmune disease, wherein said autoimmune disease is characterized by the presence in the serum of patients, of anti-CV2 auto-antibodies, which bind specifically to the polypeptide of SEQ ID NO: 8, wherein said method comprises contacting a sample isolated from a subject with the polypeptide of SEQ ID NO: 8. Claims 14 and 20-24 also encompass a method for the diagnosis of *any* type of tumor, wherein said method comprises contacting a sample isolated from a subject with the polypeptide of SEQ ID NO: 8. Finally, claims 14 and 20-24 encompass a method for the diagnosis of *any* type of paraneoplastic neurological syndromes and also *any* type of tumor, wherein said method comprises contacting a sample isolated from a subject with the polypeptide of SEQ ID NO: 8.

Claims 25-29 encompass a method for the diagnosing *any* type of tumor, wherein said method comprises contacting a sample isolated from a subject with the polypeptide of SEQ ID NO: 8.

Claims 30-32 are drawn to a diagnostic substrate for use in identifying anti-CV2 antibodies *in a subject*, wherein said substrate comprises a solid support, wherein said solid support comprises the animal's (i.e., subject's) brain; but, because Applicants probably did not intend to claim the brain in an animal, the claims are interpreted to read on an *in vivo* method for diagnosis of *any* type of paraneoplastic neurological syndrome and/or *any* type of tumor in a patient or other subject, albeit with all the steps omitted. However, it seems that because there is no obvious method by which the complex of endogenous POP-66 (i.e., the polypeptide of SEQ ID NO: 8) and endogenous anti-CV2 antibodies can be detected and because the specification does not teach such a method, the invention is not enabled. It should be noted that if Applicants intended to

claim a diagnostic method comprising contacting the animal's brain with detectably labeled antibodies, the claims would then read on a non-elected invention.

The specification teaches that Honnorat, et al (*Journal of Neurology, Neurosurgery, and Psychiatry* **61**: 270-278, 1996) identified an autoantibody in patients diagnosed with various types of paraneoplastic neurological syndromes (PNS) (paragraph bridging pages 2 and 3). Honnorat, et al teach that PNS are "rare inflammatory disorders of the central and peripheral nervous system" (citation number omitted) (page 270, column 1). Honnorat, et al teach that diagnosis of tumors has facilitated diagnosis of PNS in patients having neurological disorders suspected of having PNS (page 270, column 1). Honnorat, et al disclose that autoantibodies, which are designated anti-CV2 antibodies, were identified in the serum of eleven patients, each of whom had been or were later diagnosed with cancer (abstract; page 272, Table; and page 278, column 1). Of those eleven patients that were found to have in their sera anti-CV2 antibodies or anti-Hu antibodies, as was the case in one of the eleven, Honnorat, et al further disclose, "five patients had cerebellar degeneration, three had limbic encephalitis, two had encephalomyelitis, and one had Lambert-Eaton myasthenic syndrome" (abstract). The specification reiterates the findings and teachings of Honnorat, et al and in particular teaches that the purified antigen to which human anti-CV2 antibodies bind is a 66 kDa protein, which is expressed in rat brain cells (pages 19-21, Example 1). The specification teaches a method for isolating a cDNA molecule, which encodes the 66 kDa antigen of rat brain cells to which anti-CV2 antibodies bind (pages 21-23, Example 2). The specification discloses the polypeptide sequence (i.e., SEQ ID NO: 7) of a cDNA molecule that encodes the amino acid sequence (i.e., SEQ ID NO: 8) of the human homologue of the 66 kDa antigen of rat brain cells to which anti-CV2 antibodies bind (page 25, Table 1). The specification teaches that the human homologue of the 66 kDa antigen of rat brain cells to which anti-CV2 antibodies bind is designated POP-66 or ULIP-4 (page 4, lines 20-23).

The teachings of the specification cannot be extrapolated to the enablement of the invention commensurate in scope with the claims because in the absence of exemplification and sufficient guidance that is commensurate in scope with the claims,

one skilled in the art would not be able to practice (i.e., make and/or use) the claimed invention commensurate in scope with the claims with a reasonable expectation of success without first performing extensive and undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

In view of the teachings of Honnorat, et al, which are reiterated in the specification, one skilled in the art might reasonably predict that a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 8 could be made and used to diagnose cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome, wherein the development of said pathology is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence in the serum of the patient, of anti-CV2 autoantibodies, which bind specifically to the polypeptide of SEQ ID NO: 8. However, the specification does not exemplify the production or use of the claimed pharmaceutical compositions to diagnose, prevent, suppress, or treat *any* type of paraneoplastic neurological syndrome and/or any type of tumor. Furthermore, the specification provides insufficient guidance, which would if present, serve to instruct the skilled artisan to make and/or use the invention commensurate in scope with the claims. Certainly in absence of exemplification commensurate in scope with the claims, one skilled in the art would not accept the assertion that the invention can be used to diagnose, prevent, suppress, or treat *any* type of paraneoplastic neurological syndrome and/or any type of tumor, because the art is highly unpredictable. Accordingly, based only upon the instant disclosure, one skilled in the art cannot predict whether the invention can be used to effectively diagnose, prevent, suppress, or treat *any* type of paraneoplastic neurological syndrome and/or any type of tumor. The utility of the invention can only be ascertained

empirically and therefore one skilled in the art cannot practice the invention with a reasonable expectation of success without first performing extensive and undue experimentation.

Honnorat, et al (cited supra) teach that the serum and cerebrospinal fluid (CSF) of 45 patients diagnosed with PNS was analyzed to determine the presence or absence of anti-CV2 antibodies (page 270, column 2). Additionally, Honnorat, et al discloses that the serums of 900 patients with various inflammatory or non-inflammatory neurological disorders were also analyzed. Of the specimens obtained from those 45 patients that had been previously diagnosed with PNS, Honnorat, et al found that only eleven had anti-CV2 antibodies; the other patients either had no detectable anti-nervous system antibodies or else had well-known autoantibodies that bind antigens other than POP-66/ULIP-4 (page 272, column 2). One of the eleven patients had anti-Hu antibodies in addition to having anti-CV2 antibodies and another had anti-VGCC antibodies in addition to having anti-CV2 antibodies (page 272, Table). The patients that had detectable a level of anti-CV2 antibodies in their serum had been diagnosed with cerebellar degeneration, limbic encephalitis, encephalomyelitis, or Lambert-Eaton myasthenic syndrome (page 272, column 2). Therefore, one skilled in the art might reasonably conclude that the invention possibly could be used to diagnose cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome, wherein the development of said pathology is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence in the serum of the patient, of anti-CV2 autoantibodies, which bind specifically to the polypeptide of SEQ ID NO: 8. On the other hand, in regard to the patients that had other autoantibodies in addition to having anti-CV2 antibodies (i.e., Nos. 5 and 9), one skilled in the art would not immediately conclude upon the basis of the disclosure alone that the presence of anti-CV2 antibodies is necessarily diagnostic of frontal dementia associated with cerebellar degeneration, as with which patient No. 5 had been diagnosed, or Lambert-Eaton myasthenic syndrome, as with which patient No. 9 had been diagnosed. Moreover, one skilled in the art would have no reason to expect the invention could be used to diagnose any other PNS with the possible exceptions of

cerebellar degeneration, limbic encephalitis, encephalomyelitis, and Lambert-Eaton myasthenic syndrome wherein the development of said pathology is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence in the serum of the patient, of anti-CV2 autoantibodies, which bind specifically to the polypeptide of SEQ ID NO: 8.

Furthermore, Honnorat, et al teach that each of the patients that had been previously diagnosed with PNS and whom had a detectable level of anti-CV2 antibodies in their serum had also been previously diagnosed with cancer or were diagnosed with cancer after the analysis of the patient's serum. Honnorat, et al state, "in four cases investigated before discovery of the tumour, the detection of anti-CV2 antibodies predicted the presence of cancer" in those patients (page 277, column 1). In disagreement, however, there is no factual scientific evidence to support the conclusion of Honnorat, et al that the presence of anti-CV2 antibodies is diagnostic of a tumor, certainly not a tumor of any type. Clearly, one skilled in the art would not expect that the invention could be used to diagnose breast cancer, for example, because there is no suggestion in the art that the etiology of breast cancer is associated with autoimmunity, *per se*. Nevertheless, because there is no correlative clinical data of statistical significance that suggests that the presence of anti-CV2 antibodies is indicative of a tumor. In the absence of this essential data, which can only be acquired by further experimentation, the skilled artisan would not be able to practice the invention commensurate in scope with the claims with a reasonable expectation of success.

Tockman, et al (*Cancer Research* **52** (No. 9 supplement): 2711s-2718s, 1992) teach considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to diagnosis of any type of cancer. Tockman, et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (abstract). Early stage markers of carcinogenesis have clear biological plausibility as

markers of preclinical cancer and **if validated** can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, these must be validated against acknowledged disease end points; and, the marker predictive value must be confirmed in prospective population trials (page 2716, column 2). Therefore, in view of the teachings of Tockman, et al, it is clear that extensive and undue experimentation would be required before one skilled in the art could readily use the invention to diagnose a patient with a reasonable expectation of success.

If applicable, among the reasons that claims 9, 14-17, and 20-35 fail to meet the enablement requirement of 35 USC § 112, first paragraph are those which have previously been set forth in the 35 USC § 112, first paragraph rejection of claim 10 above. The specification, while being enabling for a method for using the polypeptide of SEQ ID NO: 8 or derivative thereof to detect the presence of anti-CV2 antibodies in a biological sample, wherein said sample is blood serum or cerebrospinal fluid (CSF), does not reasonably provide enablement for a method for using any fragment of the polypeptide of SEQ ID NO: 8 or a nucleic acid molecule comprising the polynucleotide sequence of SEQ ID NO: 7 to detect the presence of anti-CV2 antibodies in any biological sample.

As stated above, however, many of the claims (i.e., claims 9, 15, 16, 17, and 30-35) are not limited to a composition for use *in vitro*, wherein said composition comprises the polypeptide of SEQ ID NO: 8 or a derivative thereof; nor are many of the claims limited to a method for using said composition to provide an *in vitro* diagnosis of PNS and/or cancer. Clearly, many of the claims encompass an *in vivo* method for diagnosis.

Claims 16 and 17 also encompass a method for preventing, suppressing, and/or treating PNS and/or a tumor in a patient. However, the *in vivo* methods are not exemplified in the specification and one skilled in the art cannot predict whether the claimed methods can be used effectively. One cannot extrapolate the teachings of the specification to the enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with the claims, because it is well known that the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs).

Although the teachings of Bergers, et al (*Current Opinion in Genetics and Development* **10**: 120-127, 2000) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger, et al. Bergers, et al teach, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers, et al, disclose that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers, et al comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers, et al also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering a pharmaceutical composition purported to have a desired pharmacological effect to a subject. The efficacy of any

unproven drug must be determined empirically and such empirical determinations must be commensurate in scope with its expected and indicated uses.

While the therapeutic indications of the claimed pharmaceutical agents are not explicitly disclosed in the specification, because the biologic function of POP-66/ULIP-4 has yet to be determined (page 23, lines 22 and 23), it is clear that Applicants have contemplated the potentially therapeutic use of the polypeptide and antigenic fragments thereof to stimulate an antitumor immune response in a patient (pages 13-15). In other words, the Applicants have speculated that the invention might be found to be useful as a cancer vaccine. Bodey, et al (*Anticancer Research* **20**: 2665-2676, 2000) teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). In the abstract Bodey, et al disclose:

> Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research* **7**: 46-49, 1995) reviews the thinking in the art of cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell, et al further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later

growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). In addition, Spitler (*Cancer Biotherapy* **10**: 1-3, 1995) recognizes the lack of predictability of the nature of the art when she states, "ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1). Obviously, there is considerable unpredictability in the art of cancer vaccines, in general.

Bodey, et al teach that despite promising, even tantalizing results *in vitro* and *in vivo*, especially with animal models, the failure of cancer vaccines is predicated by very relationship between the tumor and the host immune system, which effectively makes the use of cancer vaccines futile:

> Malignant tumors undergo constant microevolution. Natural selection of the most advantageous surface IP [immunophenotype] involves constant modulation of previous IPs. Progressive dedifferentiation characterizes all neoplastically transformed cells. During this process, numerous 'novel' cell surface antigens appear, are modified and thus do not present the host's immune system with some immunogenic elements. The leukocytic inflammatory infiltrate contains cells with divers capabilities including neutrophils, macrophages and other professional APCs [antigen-presenting cells], as well as T lymphocytes. In situ activation of TAA [tumor-associated antigen] specific CTL [cytotoxic T-lymphocyte] clones occurs and thousands of tumor cells are lysed. However, as we would expect from any population in danger of extinction, the cells of the neoplastically transformed mass proceed with their microevolution and numerous clones of tumor cells survive each repeated attack by the immune system through secretion of immunoinhibitory cytokines, downregulation of MHC molecules, loss of costimulatory molecules, and induction of clonal T cell anergy, among other as yet uncovered ways. This process continues until the 'creation' (ironically as it may sound, by the host's immune system) of highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells. This is the reality of cancer progression: a back-and-forth struggle between host and tumor, with evolutionary dynamic exchanges throughout the entire process. Use of cancer vaccines to stimulate the immune system may be in vain" (citations omitted) (pages 2673-2674).

In summary, the specification provides no factual evidence that the claimed compositions can be used effectively to diagnose, prevent, suppress, or treat PNS and/or cancer in a patient or animal. Therefore, because of the demonstrated unpredictability in the art, in the absence of sufficient exemplification and guidance, one

skilled in the art cannot practice the claimed method with a reasonable expectation of success. Consequently, one would be forced into undue experimentation to practice the invention commensurate in scope with the claims with a reasonable expectation of success.

16. Claims 1-7, 9, 10, 14-17, and 20-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 are drawn to an isolated polypeptide, which comprises the amino acid sequence set forth in SEQ ID NO: 8, which is encoded by the polynucleotide sequence of SEQ ID NO: 7, a vector comprising said polynucleotide sequence, and host cell comprising said vector. Claim 9 is drawn to a composition useful for the diagnosis of a genus of paraneoplastic neurological syndromes and/or the early diagnosis of the formation of a genus of tumors, wherein said composition comprises the polypeptide of SEQ ID NO: 8. Claim 10 is drawn to the use of the polypeptide of SEQ ID NO: 8, a derivative of the polypeptide of SEQ ID NO: 8, or biologically active fragment of the polypeptide of SEQ ID NO: 8 to detect the presence of anti-CV2 antibodies in a biological sample. Claim 14 is drawn to a method for diagnosis of a genus of paraneoplastic neurological syndromes and/or early diagnosis of the formation of a genus of tumors, wherein said method comprises contacting a blood sample with the purified polypeptide of SEQ ID NO: 8. Claim 15 is drawn to a kit for the diagnosis of a genus of paraneoplastic neurological syndromes and/or the early diagnosis of the formation of a genus of tumors, wherein said kit comprises the polypeptide of SEQ ID NO: 8, a derivative of the polypeptide of SEQ ID NO: 8, or biologically active fragment of the polypeptide of SEQ ID NO: 8. Claims 16 and 17 are drawn to a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 8, a derivative of the polypeptide of SEQ ID NO: 8, or biologically active fragment of the polypeptide of SEQ ID NO: 8. Claims 20-29 are drawn to a method for diagnosis comprising contacting a

biological sample with the polypeptide of SEQ ID NO: 8, a derivative of the polypeptide of SEQ ID NO: 8, or biologically active fragment of the polypeptide of SEQ ID NO: 8. Claims 30-32 are drawn to a diagnostic substrate comprising animal brain. Claims 33-35 are drawn to a diagnostic kit comprising the polypeptide of SEQ ID NO: 8, a derivative of the polypeptide of SEQ ID NO: 8, or biologically active fragment of the polypeptide of SEQ ID NO: 8.

The written description is confusing; the written description includes more than one disparate disclosure, as was previously indicated above. The claims are each drawn to a genus; no one species is adequately described however. For example, claim 3 is specifically drawn to a nucleic acid molecule that encodes a polypeptide of SEQ ID NO: 8; therefore, the claim encompasses a genus of nucleic acid molecules, including genomic DNA (i.e., a gene), mRNA, and cDNA. The specification only sets forth the polynucleotide sequence of a cDNA molecule encoding the polypeptide of SEQ ID NO: 8, but in light of the specification, it is unclear that SEQ ID NO: 8 actually encodes POP-66/ULIP-4. Nevertheless, the specification fails to describe the physical features of a sufficient number of species to reasonably convince one skilled in the art that Applicants had possession of the invention at the time the application was filed. The written description, thus, fails to meet the requirements of 35 USC § 112, first paragraph.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 1-7, 9, 10, 14-17, and 20-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7, 9, 10, 14-17, and 20-35 are indefinite or vague and indefinite for numerous reasons, only a few of which are set forth below:

Claims 16, 17, and 20-35 are indefinite because the claims use of the designations "POP-66" or "ULIP" as the sole means of identifying the polypeptide to

which the claims refer. The use of laboratory designations only to identify a particular polypeptide renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Amendment of the claims to include the amino acid sequence of the polypeptide by reference to a specific sequence identification number can obviate this rejection, because the amino acid sequence of a polypeptide is unique identifier that unambiguously defines a given polypeptide.

Claim 17 is indefinite because the claims recites the limitation "according to claim 15". The use of the limitation renders the claim indefinite because there is no antecedent basis for "pharmaceutical composition" in the claim 15.

Claims 31 and 32 are indefinite because the claims recite the limitation "the substrate of claim 27". There is insufficient antecedent basis for this limitation in the claim 27.

Claims 34 and 35 are indefinite because the claims recite the limitation "the kit of claim 29". There is insufficient antecedent basis for this limitation in the claim 29.

Claims 9, 14, 15, and 20-24 are vague and indefinite because claims 9, 14, 15, 20, 23, and 24 recite the phrase "a paraneoplastic neurological syndrome" or "a paraneoplastic syndrome". The use of the phrase(s) renders the claims vague and indefinite because it is unclear to which paraneoplastic neurological syndromes the claims refer. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 25-29 are vague and indefinite because claims 25, 28, and 29 recite the limitation "a tumor of cancerous origin". Generally, a tumor is of cancerous origin. Therefore, the use of the limitation renders the claims vague and indefinite because it is unclear what subject matter the limitation is meant to include and/or what subject matter the limitation is meant to exclude. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

20. Claims 1-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Hamajima, et al (*Gene* **180**: 157-163, 1996).

Claims 1 and 2 are drawn to a purified polypeptide comprising the amino acid sequence of SEQ ID NO: 8 (claim 1), wherein said polypeptide is designated POP-66 (claim 2). Claims 3-5 are drawn to an isolated nucleic acid molecule comprising a sequence encoding the polypeptide of claim 1 (claim 3), wherein said nucleic acid molecule comprises the polynucleotide sequence set forth in SEQ ID NO: 7 (claim 4 and 5). Claim 6 is drawn to an expression or cloning vector comprising the sequence of the nucleic acid molecule of claim 3.

The specification teaches a partial sequence of the claimed polypeptide in Figure 12, which according to the description of Figure 12 the amino acid sequence in the figure corresponds to SEQ ID NO: 8 (page 18, lines 20-22). The specification teaches that the amino acid at position 56 of the amino acid sequence of Figure 12 is almost certainly a lysine (page 18, lines 23-30).

Hamajima, et al teach an isolated nucleic acid molecule that encodes an amino acid sequence that is identical to the amino acid sequence of Figure 12 (abstract), provided that Applicants' speculation that the amino acid at position 56 of their amino

acid sequence is a lysine is correct. Honnorat, et al teach that the nucleic acid molecule was cloned into a vector (page 158, column 1).

Therefore, the prior art nucleic acid molecule and the protein that is encoded by said nucleic acid molecule is deemed the same as the nucleic acid molecule and protein of the instant claims, absent a showing of any differences. The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural, and functional characteristics of the claimed product or would not function identically as the claimed nucleic acid and the protein encoded thereby. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed nucleic acid molecule and the protein encoded thereby are functionally different than those taught by the prior art and to establish patentable differences. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Board of Patent Appeals and Interferences).

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamajima, et al (*Gene* **180**: 157-163, 1996).

An analysis of claims 1-6 is set forth in the preceding 35 USC § 102(a) rejection. Claim 7 is drawn to a host cell transfected by a vector according to claim 6.

Hamajima, et al teach that which is set forth above, but do not explicitly teach a host cell transfected by a cloning and/or expression vector comprising the nucleic acid

molecule that encodes the protein that is deemed the same as the protein of the instant claims.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that Hamajima, et al would have had to transfect a host cell with the vector comprising the cDNA molecule encoding the protein that is deemed the same as the protein of the instant claims.

23. Claims 9, 10, 14, 15, 20-24, and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honnorat, et al (*Journal of Neurology, Neurosurgery, and Psychiatry* **61**: 270-278, 1996) and Antoine, et al (*Journal of Neurological Sciences* **117**: 215-223, 1993) in view of US Patent Nos. 5,770,381-A and 6,066,475-A.

Claim 9 is drawn to a composition useful for the diagnosis of paraneoplastic neurological syndromes (PNS) and/or the early diagnosis of the formation of tumors, wherein said composition comprises a polypeptide of SEQ ID NO: 8. Claim 10 is drawn to the use of a polypeptide of SEQ ID NO: 8 for detection of anti-CV2 antibodies in a biological sample. Claims 14 and 20-24 are drawn to a method for diagnosing PNS and/or cancer, wherein said method comprises contacting a biological sample isolated from a subject or patient with a polypeptide of SEQ ID NO: 8. Claims 15 and 33-35 are drawn to a diagnostic kit for use in diagnosing PNA and/or cancer, wherein said kit comprises a polypeptide of SEQ ID NO: 8.

Honnorat, et al teach the identification of anti-CV2 antibodies (abstract). Honnorat, et al that patients with paraneoplastic neurological syndromes, namely cerebellar degeneration, limbic encephalitis, encephalomyelitis, or Lambert-Eaton syndrome, had detectable levels of anti-CV2 antibodies (abstract). Honnorat, et al characterized the anti-CV2 antibodies as antibodies that bind specifically to a 66 kDa protein, which is expressed in the brain cells of rat (abstract). Honnorat, et al teach that detection of anti-CV2 antibodies is diagnostic of cerebellar degeneration, limbic encephalitis, encephalomyelitis, or Lambert-Eaton syndrome, wherein the development of said pathology in a patient is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence in the serum of the

patient, of anti-CV2 autoantibodies, which bind specifically to the 66 kDa protein of rat brain cells (abstract and pages 277-278). Honnorat, et al teaches that the study was prompted by the discovery disclosed by Antoine, et al (page 270, column 2). Antoine, et al discovered two patients diagnosed with PNS had antibodies that immunohistochemically reacted with sections of rat brain (abstract). Antoine, et al also determined that the antiserum of the patients reacted with section of human brain (page 219, column 2). Antoine, et al further disclose that the patients' antibodies reacted with several different polypeptides isolated from human brain cells; one of which was approximately the same size as the 66 kDa polypeptide of rat brain cells to which the anti-CV2 antibodies of Honnorat, et al bind (page 220, Figure 4). Furthermore, Antoine, et al show that the patients' antiserums reacted with a protein expressed in rat brain cells, which also is of approximately the same molecular mass as the protein of Honnorat, et al (page 221, paragraph bridging the columns).

Honnorat, et al and Antoine, et al do not explicitly teach a protein isolated from human brain to which the anti-CV2 antibodies of Honnorat, et al bind. Honnorat, et al and Antoine, et al do not explicitly teach a method for diagnosing PNS and/or cancer, wherein said method comprises contacting a biological sample isolated from a patient or other subject with a protein isolated from human brain to which the anti-CV2 antibodies of Honnorat, et al bind. Honnorat, et al also do not teach a diagnostic kit comprising a protein isolated from human brain to which the anti-CV2 antibodies of Honnorat, et al bind. Nevertheless, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conclude that the anti-CV2 antibodies of Honnorat, et al bind to a protein expressed in human brain cells, which is approximately the same size as the 66 kDa protein isolated from rat brain cells to which the antibodies bind, because Antoine, et al teach that the antibodies bind both rat brain and human brain and also that the antibodies bind a protein of approximately the same size in both rat brain and human brain. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conclude that protein expressed in the human brain to which the anti-CV2 antibodies bind would be very similar, if not identical to the 66 kDa polypeptide expressed in rat brain to which the

antibodies bind, because one of ordinary skill in the art knows that an antibody that has cross-reactivity binds similar or identical antigens expressed in the cross-reactive tissues. Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to clone a cDNA molecule encoding the polypeptide expressed in human brain to which the anti-CV2 antibodies bind, because identification of the polypeptide is essential to understanding pathology associated with the anti-CV2 antibodies and because conventional and routine methodology could be employed to do so since the rat homologue of the human protein to which the antibodies bind had already been isolated and characterized. One of ordinary skill in the art, thus, would have been motivated to clone the human cDNA encoding the polypeptide to which the anti-CV2 antibodies bind, because a cDNA encoding the polypeptide could be used to gain an understanding of the pathology associated with anti-CV2 antibodies and of course, to produce the polypeptide, which could be used as a tool in further experimentation aimed at this goal. Furthermore, one of ordinary skill in the art at the time the invention was made would have been motivated to clone the human cDNA molecule, because based upon the teachings of Honnorat, et al, in particular, one of ordinary skill in the art at the time the invention was made would have had the additional incentive that the polypeptide produced by the isolated human cDNA could be used to develop a diagnostic protocol, wherein a patient could be diagnosed with cerebellar degeneration, limbic encephalitis, encephalomyelitis, or Lambert-Eaton syndrome, wherein the development of said pathology in the patient is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence in the serum of the patient, of anti-CV2 autoantibodies, because Honnorat, et al teach that the detection of anti-CV2 antibodies is indicative of said pathologies.

US Patents Nos. 5,770,381-A and 6,066,475-A teach methods for diagnosing autoimmune disease associated with the development of autoantibodies in the patients, wherein said methods comprise contacting a sample of blood serum, comprising the patients' antibodies, with the protein to which the autoantibodies bind and detecting the formation of the complex of the protein and the autoantibodies, whereby said detection of the complex is diagnostic, since the presence of the autoantibodies is indicative of

the pathology to be diagnosed. US Patents No. 5,770,381-A teaches a diagnostic kit comprising the protein antigen to which the autoantibodies bind (column 4, lines 8-15).

Therefore, in view of the teachings of Honnorat, et al, Antoine, et al, and the teachings of US Patents Nos. 5,770,381-A and 6,066,475-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to clone a cDNA molecule encoding the polypeptide expressed in human brain to which the anti-CV2 antibodies bind, produce the polypeptide, develop a diagnostic assay for diagnosing cerebellar degeneration, limbic encephalitis, encephalomyelitis, or Lambert-Eaton syndrome, wherein the development of said pathology in a patient is contingent upon the patient having had developed an autoimmune disease, which is characterized by the presence in the serum of the patient, of anti-CV2 autoantibodies, and to produce a kit comprising the polypeptide or a composition comprising the polypeptide or a solid support comprising the polypeptide, because the combined teachings of Honnorat, et al, Antoine, et al, and US Patents Nos. 5,770,381-A and 6,066,475-A would have provided one of ordinary skill in the art with sufficient guidance in view of conventional knowledge in the art to do so and also would have provided one of ordinary skill in the art with sufficient incentive to do so. However, it is further noted that there had been a long-felt need in the art for better diagnostic assays, which could be used to diagnose pathologies associated with the development of autoantibodies, namely anti-CV2 antibodies, because Honnorat, et al and Antoine, et al teach that anti-CV2 antibodies are associated with pathology.

Conclusion

24. No claims are allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
September 21, 2001

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